

## Research Article

# Formulation and Pharmaceutical Assessment of *Annona muricata* Oral Capsules and Suspension as Antidiarrhea Dosage Forms

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*Annona muricata* (Annonaceae) is a tropical plant widely known for its edible fruits. Recent scientific studies have confirmed the folkloric use of its seeds as an antidiarrheal agent. This study sought to formulate capsules and suspensions using the ethanolic extract from *Annona muricata* seeds. The dried ethanolic extract was formulated into granules and subsequently encapsulated. The suspension formulated was assessed for sedimentation rate, sedimentation volume, viscosity, dissolution, drug content, and flow rate, while pharmacopeia tests such as disintegration, dissolution, uniformity of weight, and drug content were carried out on the formulated capsules. The formulated suspension passed the drug content and in vitro release studies. *Annona muricata* suspension exhibited pseudoplastic flow with good sedimentation rate and sedimentation volume. The formulated capsules passed the in vitro dissolution studies, weight uniformity, disintegration, and drug content tests. The ethanolic extract of *Annona muricata* seeds was appropriately formulated into standardized solid and liquid oral dosage forms.

## 1. Introduction

Diarrhea is a condition of having unusual loose or watery stools with a sense of urgency. It is also known to occur when the lining of the intestine is unable to retain fluid, leading to loose stool. The precarious nature of the disease is linked with dehydration due to fluid loss and consistently high morbidity in the absence of vigorous interventions. Diarrhea is a leading cause of death in all age groups with an estimated 1.31 million deaths recorded annually across the globe for a mortality rate of 7.58% [1, 2]. The burden of deaths is greatest in low-income countries such as Ghana where

getting access to portable water and proper sanitation is a problem. In Ghana, the mortality rate as at 2020 was 7.15% per 1000 inhabitants with diarrhea accounting for about 25% of death in children under five years with correspondingly high debilitating effects in adults [1–4].

Most patients with diarrhea do not seek medical attention unless symptoms last for more than three days or they have coexisting fever, prostration, or rectal bleeding by which time their condition may have worsened. Hence, it is very imperative that medications used in the treatment of diarrhea are effective and readily available [1, 3]. In order to treat diarrhea, various orthodox medicines have been

developed. However, the World Health Organization promotes studies on medicinal plants that can be used to manage and treat diarrhea and to formulate these medicinal plant extracts in standardized dosage forms that will be convenient, efficient, and safe for the patient. In Ghana, traditionally, a lot of plants are used to treat diarrhea including *Bridelia ferruginea*, *Albizia ferruginea*, and *Psidium guajava* (guava). Another plant commonly used to treat diarrhea in Ghana is *Annona muricata* [5–7].

*Annona muricata* of the family Annonaceae, popularly known as soursop, graviola, or guanabana is a fruit that grows in the tropical regions of America, Africa, and the Caribbean. Phytochemical studies carried out on various parts of the plant revealed the presence of tannins, phenolic compounds, flavonoids, and alkaloids which underpin their pharmacological relevance [6, 8]. Further research carried out by Doe et al. shows that the ethanolic extract of the seeds have antidiarrheal property and corroborates its folkloric use [9]. Irrespective of the reported dose and pharmacological activity of the ethanolic extract of the seeds of *Annona muricata* in the management of diarrhea, its use is limited in clinical settings due to the absence of standardized dosage forms. Against this background, this study seeks to provide standardized dosage forms (suspensions and capsules) of the ethanolic extract of the seeds of *Annona muricata* in order to substantiate its clinical usefulness and integration into current health care delivery as an effective antidiarrheal agent.

## 2. Materials and Methods

**2.1. Materials.** *Annona muricata* fruits (Ashaiman, Ghana), maize starch (Anhui Sunhere Pharmaceuticals, China), acacia and tragacanth powder (Sigma Aldrich), benzoic acid, and laboratory grades of concentrated hydrochloric acid and ethanol (Department of Pharmaceutics, KNUST, Ghana) were obtained.

### 2.2. Methods

**2.2.1. Collection of Sample and Extractive Procedure.** *Annona muricata* fruits were obtained from the Ashaiman market, in the Greater Accra region of Ghana, and authenticated at the Department of Pharmacognosy, KNUST, Kumasi, Ghana. Extraction was done using a previously established method [9]. The seeds were removed from the fruits. It was then dried under shade for 7 days, and the weight was taken afterwards. The dried seeds were milled into fine powder and weighed as well. The milled seeds were then macerated in 80% ethanol in an airtight container and stored in the refrigerator at 5°C for 7 days. The decanted solution was filtered using a filter paper, and the filtrate was evaporated using a rotary evaporator and then freeze dried into fine powder.

**2.2.2. Assessment of the Flow Characteristics.** The indirect method described by Aulton and Taylor [10] in the characterization of the flow properties of materials was used.

**2.3. Formulation of *Annona muricata* Suspension.** In the formulation of 100 mL suspension, *Annona muricata* extract was weighed and added to the previously weighed *Acacia* and triturated with benzoic acid and double strength chloroform water to obtain a uniform mixture (such that each 5 mL contains 0.15 g). Water was then used to top up to the mark (Table 1). The excipients were selected after several preformulation studies with different excipients.

**2.4. Formulation of *Annona muricata* Granules.** In preparing the granules, starch, lactose, and *Annona muricata* extract were weighed and mixed using geometric dilution (Table 2). The powdered mixture was then blended with tragacanth mucilage to form a damp mass and prepared into granules (14.8 g) using the method described by [10]. The excipients were selected after several preformulation studies with different excipients.

**2.5. Evaluation of Flow Properties of *Annona muricata* Granules.** The flow properties of the formulated granules were determined using the fixed height method for angle of repose and bulk density measurements (Hausner ratio and Carr's index) [10].

**2.6. Encapsulation of *Annona muricata* Granules.** The granules were encapsulated using capsule size 1 with 0.15 g of extract in each capsule (150 mg per dose). Fifty-five (55) capsules were filled simultaneously.

**2.7. Quality Assessment of Formulated Capsules.** The weight uniformity and disintegration tests were determined as described by the British and International Pharmacopeias [11, 12].

**2.7.1. Drug Content.** Ten capsules were used for this experiment. A capsule was emptied, and 20 mL of 0.1 M HCl was added. The mixture was filtered, and 0.1 M HCl was used to top it up to 50 mL. Drawell's UV spectrometer was used in measuring the absorbances at 300 nm after serially diluting the solutions. The recorded absorbance was then inserted into a calibration equation, and the percentage content was determined for each capsule [11, 13–15].

**2.7.2. In Vitro Dissolution Test.** In vitro dissolution study was done using the USP type I basket dissolution apparatus. 900 mL of 0.1 M HCl was transferred into each of the six dissolution vessels, the temperature of the dissolution vessel was maintained at  $37 \pm 2^\circ\text{C}$ , and a randomly selected capsule was dropped into the dissolution medium. An aliquot of the sample was withdrawn at regular time intervals (5, 15, 30, 35, 40, 45, and 60 minutes), and the same volume of 0.1 M HCl was used to replace the volume withdrawn. The samples were filtered and analyzed with the UV spectrometer at 300 nm. The absorbances obtained were inserted into the calibration equation to obtain the amount of drug released at each time point. A graph of cumulative drug released against time was then plotted to obtain the dissolution profile of the formulated capsules in 0.1 M HCl [11, 13–15].

TABLE 1: Formula for preparing *Annona muricata* suspension.

Ingredient	Quantity
<i>Annona muricata</i> extract	3 g
Acacia powder	3 g
Benzoic acid	0.1 g
Double strength chloroform water	50 mL
Water	100 mL

TABLE 2: Formula for preparing *Annona muricata* capsules.

Ingredient	Quantity (g)
<i>Annona muricata</i> extract	10
Starch	3.2
Lactose	0.5
Tragacanth mucilage (10 % <sup>w/v</sup> )	0.7

### 2.8. Quality Assessment of *Annona muricata* Suspension.

The appearance, pH, rheology, apparent viscosity, drug content, in vitro dissolution studies, sedimentation volume, and sedimentation rate were determined using previously described methods [11, 16–18].

**2.8.1. Uniformity in Drug Content of Formulated *Annona muricata* Suspension.** Five (5) mL of the formulated suspension was diluted with 25 mL of 0.1 M HCl, filtered, and topped up to 50 mL using the same solvent (0.1 M HCl). Drawell's UV spectrometer was used in measuring the absorbances at 300 nm. The recorded absorbance was then inserted into the calibration equation, and the percentage content was determined. This was repeated for nine other 5 mL aliquots [11, 16–18].

**2.8.2. In Vitro Dissolution Study of *Annona muricata* Suspension.** The USP type II paddle dissolution apparatus was used with 900 mL of 0.1 M HCl (as the dissolution medium) heated to  $37 \pm 2^\circ\text{C}$ . The paddles were set to a speed of 50 rpm, and 5 mL of the prepared suspension was transferred into the dissolution medium. After 5, 15, 30, 35, 40, 45, and 60 minutes, an amount of 10 mL of the dissolution medium was withdrawn, filtered, and the absorbance at 300 nm was determined using Drawell's UV spectrometer. The withdrawn volume was replaced with same volume of 0.1 M HCl to maintain sink conditions. The absorbances obtained were inserted into the previously determined calibration equation to obtain the amount of drug released at each time point. A graph of cumulative drug released against time was then plotted to obtain the dissolution profile of the formulated suspension in 0.1 M HCl [11, 16–18].

## 3. Results and Discussion

**3.1. Flow Characteristics of Granules and Extract.** The powdered extract showed good flow properties with Hausner's ratios of 1.12, Carr's index of 10.98%, and angle of repose of  $20.5^\circ$ , while the *Annona muricata* granules exhibited excellent flow properties with Hausner's ratios of 1.10, Carr's index of 8.93%, and angle of repose of  $17.5^\circ$ . This

confirms that the formulated granules will improve the encapsulation process by enhancing the uniform filling of the capsule shells [11, 13].

### 3.2. Assessment of *Annona muricata* Capsules

**3.2.1. Capsule Weight Uniformity.** The weight uniformity of *Annona muricata* capsules as given in Table 3 complied with the weight uniformity specifications according to the International Pharmacopeia [12]. This implies that each manufactured capsule potentially has the exact amount of the *Annona muricata* extract and excipients specified, with little variability, reducing the risk of under dosing and overdosing.

### 3.2.2. Disintegration Profile of Formulated Capsules.

Based on the results given in Table 4, the formulated capsules passed the disintegration test as stipulated by the British Pharmacopeia [11]. This indicates that the capsules will release their contents within time for further dissolution of the extract to occur.

### 3.2.3. Drug Content.

The percentage drug content of all ten sampled capsules were within the standard range of 85.0–115% (Table 5) and confirms that the encapsulation process as well as other preencapsulation procedures were carried out accurately. The results also indicate that the formulated capsules will provide the required therapeutic dose without any overdose or underdosage that would be harmful or detrimental to the patient.

### 3.2.4. In Vitro Dissolution of *Annona muricata* Extract from Capsules.

According to the data (Figure 1), 99.29% of the extract was released at the 45th minute. This implies that the capsules passed the dissolution test and can dissolve well in physiological solution, allowing the extract to be absorbed and the intended pharmacological activity to be achieved [11, 13].

### 3.3. Quality Assessment of *Annona muricata* Suspension

**3.3.1. Appearance Test.** Over the course of four weeks, the formulated suspension was closely monitored for the appearance or absence of undesired physical changes. There were no unwanted physical changes in the prepared suspension (Table 6). This shows that the suspension is physically stable and retains its aesthetic attractiveness and that the excipients employed in the formulation were appropriate [10, 19].

### 3.3.2. Sedimentation Volume and Rate of Formulated Suspension.

A good suspension, in order to improve uniform and accurate dosing, should not have the suspended particles settling quickly. The sedimentation volume of an ideal suspension should be close to 1 with a correspondingly low sedimentation rate [19–21]. This property was evident in the formulated suspension (Figure 2).

TABLE 3: Weight uniformity of formulated capsules.

Quantity of capsules used	Average weight (g)	Quantity of capsules deviating by $\pm 5\%$	Quantity of capsules deviating by $\pm 10\%$
20	0.450	None	None

TABLE 4: Disintegration time of formulated capsules.

Disintegration test	1 <sup>st</sup> determination	2 <sup>nd</sup> determination	Average
Time (minutes)	2.60	2.40	2.50 $\pm$ 0.14

TABLE 5: Assay of formulated capsules.

Capsule number	Drug content (%)
1	99.32 $\pm$ 0.02
2	91.86 $\pm$ 0.03
3	101.53 $\pm$ 0.10
4	95.59 $\pm$ 0.08
5	99.32 $\pm$ 0.06
6	95.59 $\pm$ 0.05
7	101.53 $\pm$ 0.04
8	91.86 $\pm$ 0.06
9	101.53 $\pm$ 0.07
10	99.32 $\pm$ 0.04

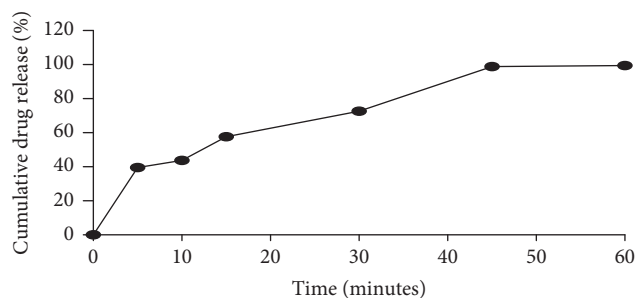
FIGURE 1: Release profile of *Annona muricata* extract from capsules.

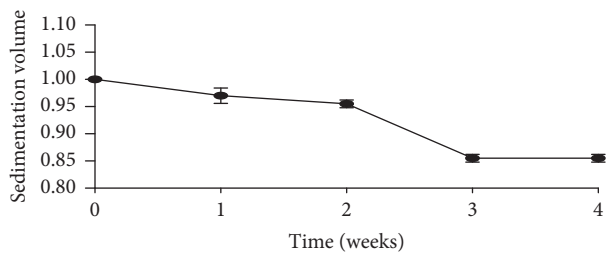
TABLE 6: Physical stability of formulated suspension.

Week	Physical instability (aggregation, caking, crystal growth formation)
1	No physical instability observed
2	No physical instability observed
3	No physical instability observed
4	No physical instability observed

3.3.3. *Rheology, Redispersibility, and pH of Formulated Suspension.* There was no statistical variation ( $P \geq 0.05$ ) in the pH of the formulated suspension (Table 7) to indicate any physicochemical change [19, 22, 23]. The flow time of the suspension was short with a correspondingly high apparent viscosity for easy pourability (Table 7) [16, 19, 22]. Throughout the study period, the solid particles were redispersed with less than ten (10) strokes (Table 7). The prepared suspension possessed pseudo-plastic flow, which implies that it may be swiftly redispersed with modest agitation, and the appropriate amount can be easily drawn (Figure 3). This feature is critical for a good suspension [24].

3.3.4. *Drug Content.* All sampled doses passed the drug content test (Table 8) [11]. This implies that each volume will have the exact amount of extract needed, preventing overdosing and underdosing, both of which are hazardous to the patient's health.

3.3.5. *In Vitro Dissolution Profile of Annona muricata Extract from Formulated Suspension.* According to the data (Figure 4), 99.20% of the extract was released at the 45th minute which complies with pharmacopeia specifications. This implies that the capsules can dissolve well in physiological solution, allowing the extract to be absorbed and eliciting the intended therapeutic effect [11, 22].

FIGURE 2: Effect of time on the sedimentation volume of *Annona muricata* suspension.TABLE 7: Physicochemical properties of *Annona muricata* suspension.

Week	pH	Flow time (s)	Apparent viscosity ( $\eta$ ) (mL/s)	Redispersibility (number of strokes)
0	$6.93 \pm 0.012^{ns}$	$8.68 \pm 0.58$	$1.153 \pm 0.28$	7
1	$6.94 \pm 0.013^{ns}$	$8.67 \pm 0.03$	$1.155 \pm 0.19$	7
2	$6.92 \pm 0.010^{ns}$	$8.73 \pm 0.50$	$1.147 \pm 0.31$	9
3	$6.93 \pm 0.016^{ns}$	$8.64 \pm 0.45$	$1.159 \pm 0.37$	7
4	$6.93 \pm 0.014^{ns}$	$8.62 \pm 0.25$	$1.161 \pm 0.09$	7

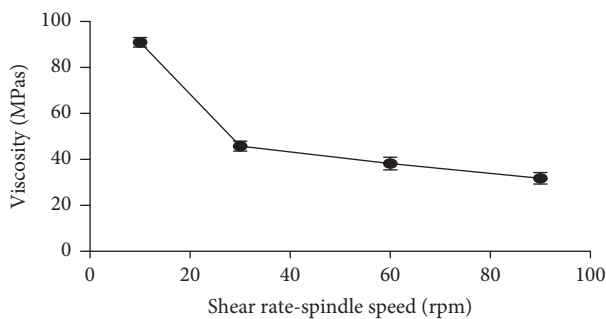
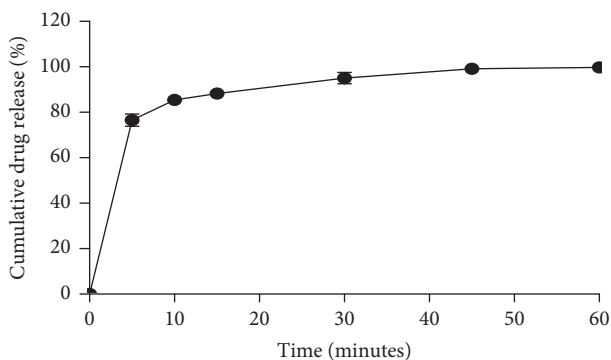


FIGURE 3: Rheology of formulated suspension.

TABLE 8: Assay of formulated suspension.

Sampled dose number	Absorbance	Drug content (%)
1	0.43	91.86
2	0.43	91.86
3	0.46	101.53
4	0.44	95.59
5	0.43	91.86
6	0.45	99.32
7	0.46	101.53
8	0.46	101.53
9	0.45	99.32
10	0.44	95.59

FIGURE 4: Release profile of *Annona muricata* extract from suspension.



#### 4. Conclusion

This study has shown that the ethanolic extract of *Annona muricata* can be successfully formulated into capsules and suspension. The prepared dosage forms satisfied the pharmacopeia requirements for quality evaluation and may be used as appropriate alternatives in the management and treatment of diarrhea.

#### Data Availability

The data used to support the findings of this study are included within the article and also available from the corresponding author upon request.

#### Conflicts of Interest

The authors declare that there are no conflicts of interest.

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